Strategies for mobile phase optimization in chromotography. A chenometrical approach.

Weijland, Jan Willem

60, (1958).
, 4, 463- 87,(1962).

SUMMARY

This thesis investigates some strategies that can be employed to design optimal mobile phases for chromatographic separations.

Optimization methods for this purpose have to cope with two major obstacles inherently connected with the chromatographic system: fuzzy definitions of the separation quality when more solutes are involved, and response surfaces that are generally not unimodal.

Apart from being a nuisance, the latter property also indicates an efficient approach to these investigations, simulation. This involves the construction of a model of relevant aspects of the chromatographic system. Useful as an important part of several optimization methods itself, modelling conveniently allows the evaluation of different approaches to the optimization of HPLC separations, while minimizing the number of experiments.

The first chapters may be viewed as a general introduction to the subject of this research.

Chapter I, - Introduction -, discusses the place of this research in the fields of chemometrics and analytical chemistry, and sets the scope.

Chapter II, - The grey box of chromatography -, explains the choice of the modifier content in the mobile phase mixture as the control variables, and treats the theoretical aspects of HPLC relevant to the mathematical modelling of the dependence of retention behaviour on mobile phase composition. It is shown that the use of quadratic polynomials to describe the dependence of the capacity factor on mobile phase composition finds some justification in theory.

Chapter III discusses mixture modelling and design. Though polynomial regression is fairly well known in analytical chemistry, and mixture modelling has been used regularly recently, little attention has been paid to the peculiarities of mixture modelling and their statistics.

Chapter IV studies the reversed phase chromatography of a set of 20 sulfonamides in three ternary mobile phase systems. Regression equations are calculated to describe the dependence of the capacity factors on mobile phase composition. Sources of error are identified and discussed. Quadratic models of log k appear to be suitable for ternary phases consisting of water/methanol/THF, but for a ternary phase with acetonitrile as a component the fits may sometimes be improved by addition of the cubic blending term.

The calculated regression equations are used in the following chapters to investigate and evaluate several approaches to the optimization problem addressed in this thesis.

In chapter V response surfaces for the separation of two mixtures of five sulfonamides are simulated, using several Chromatographic Response Functions described in the literature as the response criterion. The response surfaces obtained are multimodal, which means that sequential methods of optimization are in great danger to miss the optimum. It is

concluded that sequential optimization methods are unsuitable for application in chromatographic separations, implying that sound optimization strategies should be based on models of the chromatographic behaviour of the individual solutes.

Chapter VI discusses the window diagram method, which optimizes the separation factor of the worst separated pair. Its field of application is extended to the nonlinear models and ternary mobile phase mixtures encountered in HPLC. The method is illustrated by its application to the optimization of three ternary mobile phases for the separation of three different mixtures of sulfonamides. Sources of error are discussed, and the possibilities offered by the method to decrease the analysis time are investigated.

Chapter VII introduces the Operations Research method of nonlinear programming as a tool in the optimization of HPLC-separations, reformulating the objective to take economical considerations into account. The method appears to be promising, especially when the dimensionality of the factor space increases. Results are comparable to those obtained with the window diagram method.

Finally chapter VIII shows that the previously discussed techniques may be employed for a different chromatographic technique, with a different objective. The ternary mobile phase of a TLC-procedure for the identification of sulfonamides is optimized with respect to Information Content and MDP. Again, modelling provides the clue to succesful optimization.

SAMENVATTING

Dit proefschrift behand
maliseren van de mobiele f

Optimaliseringsmethoden
geconfronteerd met twee
objektief kriterium te de
beschrijft wanneer er meer
responsoppervlakken veelal

Deze laatste eigenscha
ciente aanpak om de versc
modelleren van het chrom
dingen in afhankelijkheid
(regressie)modellen bekend
een mengsel gesimuleerd w
liseringsalgorithmes geevalu
siemodellen tevens de basis

De eerste hoofdstukke
inleiding.

Hoofdstuk I bespreekt
bieden van de chemometh
grenzen van deze studie.

Hoofdstuk II verklaart d
mentele variabele, en beha
relevant zijn voor het mat
Aangetoond wordt dat er
gebruik van kwadratische
kelijkheid van de kapacit
mobiele fase beschrijven.

Hoofdstuk III bespreekt
neer de variabelen mengsel
sche literatuur het gebruik
worden is, wordt meestal
zich hier voordoen besteed,
normaal gebruikte regressie
kader, wordt nader op deze

In hoofdstuk IV wordt
den in drie ternaire mobiel
gebruikt voor het berekene
factoren van de sulfonam
mobiele fase mengsels. V
ceerd en besproken. Gecor
van de logarithme van de
de mobiele fase in vele ge
bestaande uit water - me
kubische 'blending'-term ver

De in dit hoofdstuk berek